

# Pharmacogenetics of Cancer and DNA Repair Enzymes

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## 1. Introduction

Pharmacogenetics is focused on finding associations between drug response and the genetic background of a patient.<sup>38</sup> Resequencing of the human genome revealed that nucleotide variation between individuals exists in 0.1% of the genome, which corresponds to 3 million differences. These variations occur in more than 1% of a population and are designated as single nucleotide polymorphisms (SNP), normally not causing any disease. Functional variants caused by SNPs in drug related genes (such as metabolism enzymes, transporters and receptors) have become of interest more and more in recent years.<sup>21,22,40,73</sup> Variations that occur less frequent than 1% are designated as mutations and could be disease causing. Pharmacogenetic research has been expanded dramatically, with 1334 publications in the past century starting from 1961, while 7654 papers have been published since the year 2000 (pubmed accession date: November 18, 2010). The ultimate goal of pharmacogenetic research is the establishment of personalized medicine, aiming in prescribing the best choice of drug with the optimal concentration.<sup>67</sup> Even the route of administration could be considered. At present, pharmacogenetics is not applied widely in clinical practice as a diagnostic tool, but is mainly restricted to research, which is, finding associations between drug response and genetic background within a group of patients. Much research is being performed in order to achieve a more beneficial cancer therapy, although pharmacogenetic research is also active in other fields like rheumatoid arthritis,<sup>7,42,52</sup> transplantation<sup>50,84</sup> and diabetes.<sup>19,51</sup>

The application of whole genome techniques for predicting patients' sensitivity or resistance to a drug is the definition of pharmacogenomics.<sup>27,68</sup>

At present, most pharmacogenetic research is focused on enzymes that control the metabolism and uptake of many clinically used drugs. Most of these drugs are metabolized by Cytochrome P450 of which variant alleles are common that affects drug effectiveness.<sup>15,24,33</sup> Roche diagnostics has developed an array to screen for the most important SNPs in Cytochrome P450 isoenzyme 2D6.<sup>72</sup> This array is the first one that is approved by FDA for diagnostic testing. Other interesting genes with relatively high frequency of variant alleles are transporters such as MDR1.<sup>5,41,70</sup> Affymetrix had developed an array (DMET) to screen for 1936 SNPs in genes that are involved in drug metabolism, uptake and detoxification.<sup>16</sup>

Although screening for SNPs in DNA mismatch repair enzymes is a standard method for diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC),<sup>45,61</sup> pharmacogenetics of DNA repair enzymes is only applied in research settings and is discussed later in this chapter.

## 2. Genetic characteristics of tumor cells

When a normal cell loses the ability to regulate its own cell division but instead continuously divides, then this cell has become a tumor cell (reviewed by Hanahan and Weinberg<sup>25</sup>). Benign tumors result from minor imbalances in tissue whereby too many genetically stable cells are produced. These cells grow expansively and since they are often encapsulated, they can be removed by surgery. Since blood cells travel throughout the body, clonal expansion of these cells never result in benign tumors, but always in malignant tumors. Malignant tumors are genetically unstable, metastasize easily and are causing cancer. These type of tumors can only be removed by surgery if they are caught in early development, but many solid tumors smaller than 1 cm have already been metastasized. Due to their genetic instability, tumor cells have different genetic characteristics and consequently a heterogeneous phenotype. In such a heterogeneous population, the cells that are best adapted to their environment survive better than the less malignant ones. Genetic alterations consist of "loss of heterozygosity", translocations, mutations and disturbance in methylation.

## 3. Platinum drugs for cancer treatment

The treatment of cancer depends fully on the type of tumor and often several approaches are made to kill the tumor. Antibodies are frequently used to block receptors that are over expressed in the tumor, or to scavenge growth stimulating factors. For example the epidermal growth factor receptor (EGFR) is essential for normal cellular function, however, increased levels of EGFR mRNA are associated with metastasis and aggressive tumor growth.<sup>39</sup> EGFR is over expressed in tumor cells and many therapies are focused on blocking this receptor using antibodies such as cetuximab or panitumumab.<sup>39,56,63</sup> On the other hand, platinum-drugs intercalate in the tumor DNA thereby inhibiting DNA replication and thus inducing cell death.<sup>8,9</sup> Platinum containing drugs such as cisplatin, carboplatin or oxaliplatin, have a broad range of activity in malignant disease and are used to treat many types of cancer. In general, the antitumor effect of platinum drugs is the result of intercalation of platinum in the DNA helix, causing the formation of platinum-DNA cross-links which ultimately leads to programmed cell death.

Cisplatin was the first platinum drug approved for the treatment of both ovarian and testicular cancer in 1978.<sup>29</sup> At present, more than 80% of patients with testicular cancer can be cured with cisplatin-based chemotherapy.<sup>31</sup> It was also applied to treat other solid tumors such as cervical, head and neck, lung and bladder cancer. Unfortunately, neither of these cancer types could be treated with a similar efficiency as accounts for testicular cancer.<sup>64</sup> Cisplatin was the most commonly used chemotherapy drug but its use is limited by severe side effects such as gastrointestinal and renal toxicities. For that reason, an analogue with less toxicity was developed that replaced cisplatin in many chemotherapeutic regimens. This second-generation platinum drug was carboplatin which has equivalent

activity, is more stable, and is less toxic than cisplatin. Especially neurotoxicity is less frequently observed when compared with cisplatin.<sup>26</sup> Additionally, loss of hearing is less frequently observed in carboplatin-treated patients than is seen in patients treated with cisplatin.<sup>10,83</sup> Carboplatin has a different spectrum of toxicity, as its primary toxic effects are hematological.<sup>78</sup> A third generation-platinum compound was oxaliplatin. Oxaliplatin shows no cross resistance with cisplatin and carboplatin which is an important benefit for the treatment of colorectal cancer. Colorectal cancer appeared extremely insensitive to cisplatin and carboplatin. Another advantage is the toxicity profile which is much less frequent, although neurotoxicity is still observed.<sup>26</sup>

Cisplatin and carboplatin, that share the same mechanism of action, are fully cross resistant and form identical lesions in DNA. The mechanism of action of oxaliplatin is different and oxaliplatin does not share cross resistance.<sup>17,44</sup>

#### 4. Platinum induced DNA damage

As mentioned above, the cytotoxic property of platinum (Pt)-drugs is the intercalation in cellular DNA, forming Pt-adducts, that consequently inhibit DNA replication and thus induce cell death.<sup>9</sup> Although Pt-based drugs are the most widely used in cancer treatment, many tumors are completely resistant to these drugs. The difference in clinical response is thought to be due, in part, to the pharmacokinetics of these drugs, as summarized by Marsh et al.<sup>53</sup> Once Pt is inside the cell, Pt-adducts are formed within the DNA and a cellular defense is activated (Figure 1). DNA is the preferential and cytotoxic target for platinating agents. Three different types of lesions can be formed: monoadducts, intrastrand crosslinks and interstrand crosslinks (Figure 2). Monoadducts are first formed, but almost all monoadducts then react to form crosslinks of which the majority is intrastrand crosslinks. Cisplatin- and carboplatin-induced crosslinks bend the DNA double helix by 32-35° toward the major groove, whereas oxaliplatin induced crosslinks bend the double helix even more.<sup>18</sup>

Oxaliplatin adducts are bulkier and more hydrophobic than those formed by cisplatin and carboplatin, leading to different effects in the cell.<sup>55,65</sup> Interstrand crosslinks induce more steric changes in DNA and are therefore considered to be more toxic. Cisplatin and oxaliplatin have been found to form the same types of adducts at the same sites on the DNA.<sup>35,58</sup> Both cisplatin and oxaliplatin form approximately 60-65% intrastrand GG, 25-30% intrastrand AG, 5-10% intrastrand GNG, and 1-3% interstrand GG diadducts.<sup>20</sup>

#### 5. DNA repair mechanisms

Platinum adducts are recognized by the cellular DNA repair system and resistance to platinum chemotherapy is achieved by activity of either the nucleotide excision repair (NER), mismatch repair (MMR) or homologous recombination (HR) pathways. On the other hand, mutations in key enzymes of these pathways result in sensitivity to platinum drugs. The nucleotide excision repair system deals with helix-distorting lesions that interfere with base pairing and obstruct transcription and normal replication. Therefore, NER is the most important pathway involved in the efficacy of platinum chemotherapeutic therapy.<sup>64</sup> NER consists of two sub-pathways, global genome NER (GG-NER) that screens the entire genome for damage, and transcription coupled repair (TCR) that screens for lesions that might block elongating RNA polymerases.<sup>76</sup> Specific protein complexes are involved in the

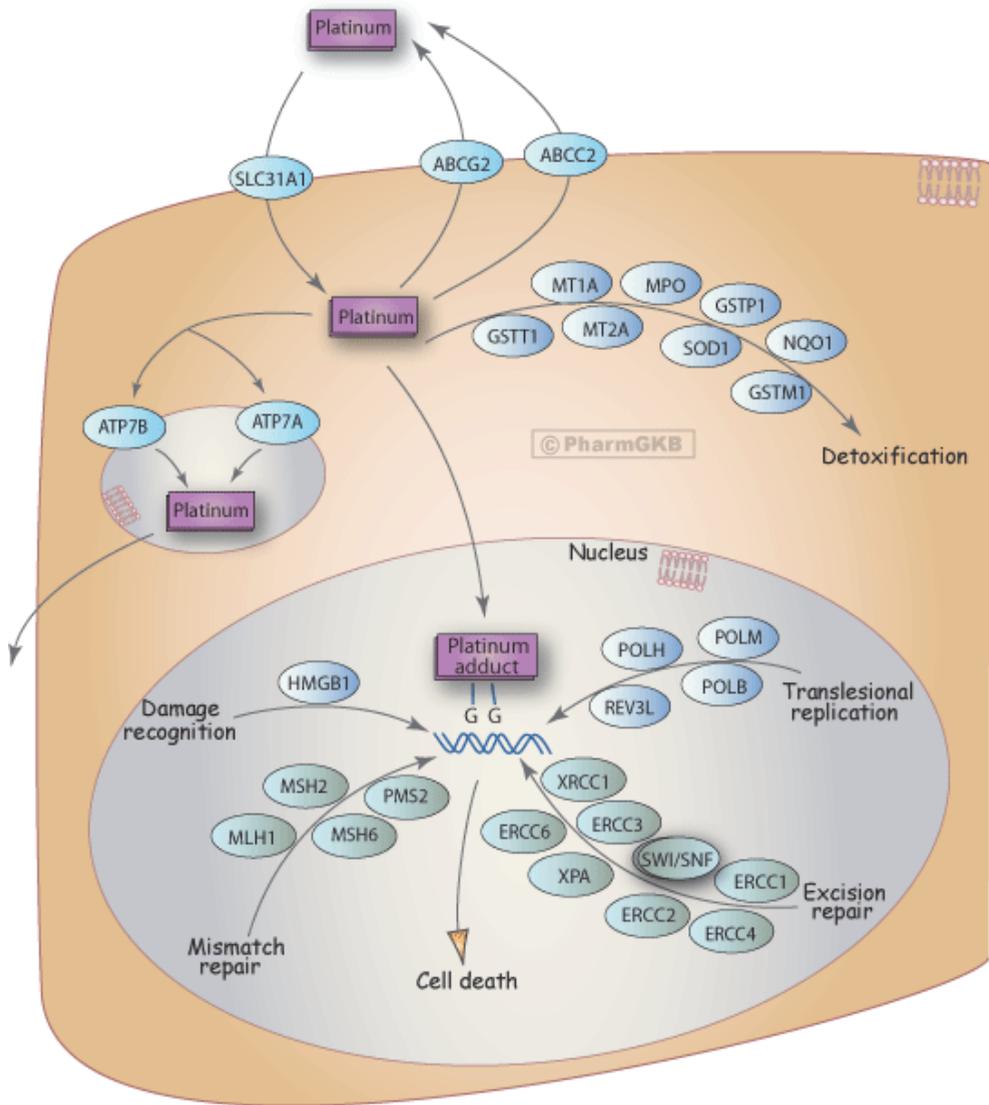


Fig. 1. Cellular response to platinum exposure. Figure taken from <http://www.pharmgkb.org/do/serve?objId=PA150642262&objCls=Pathway>. XPC, sensor for DNA damage, has not been depicted in this figure.

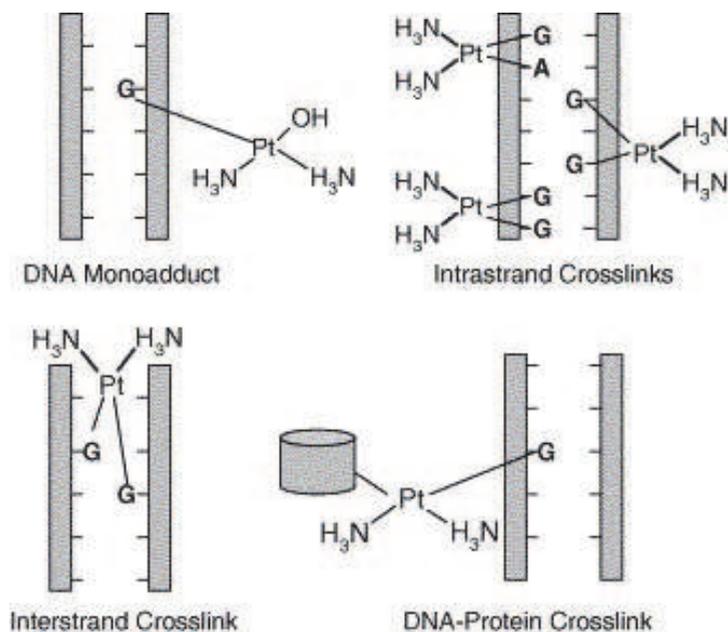


Fig. 2. Platinating agent adducts on DNA. Platinating agents are able to react with DNA to form monoadducts, intrastrand crosslinks, interstrand crosslinks and DNA-protein crosslinks. Figure taken from Rabik and Dolan.<sup>64</sup>

first step of DNA damage recognition of GG-NER and TC-NER. Nomenclature of key enzymes involved in NER is listed in table 1. In GG-NER, XPC-hHR23B screens first on the basis of disrupted base pairing instead of lesions,<sup>75</sup> explaining why mildly distorted damage is poorly repaired.<sup>75</sup> In TCR, two specific enzymes are necessary to displace the stalled polymerase to make the lesion accessible for repair, CSA and CSB.<sup>46</sup> Next steps in the NER system are identical (Figure 3). In general, the helix structure of about 30 base pairs around the damaged site, is opened by helicase XPD (part of the transcription factor TFIIH). Replication protein A binds to the undamaged site to stabilize the open DNA strands. Next, XPG and ERCC1/XPF cleave the DNA strand on both sides of the damaged site. The DNA replication machinery then completes the repair by filling the gap. In total, more than 25 proteins participate in NER and for almost all NER factors, mouse mutants have been generated<sup>14</sup> some of which show features of premature ageing. In general, mutations in key enzymes of NER (such as XPD, XPB, XPG and ERCC1) compromise NER and cause developmental delay and affect transcription.<sup>80</sup> The incidence of sun induced skin cancer is >1000 fold increased, whereas frequency of internal tumors is modestly elevated.

The presence of dinucleotide repeats in the human genome is quite common and form unstable motifs in some cancers.<sup>36</sup> This phenotype of microsatellite instability is caused by defects in MMR in the hereditary nonpolyposis colorectal cancer (HNPCC) and in a variety of sporadic cancers. Replication slippage of repetitive sequences introduce mispairing of nucleotides. These errors are removed by MMR and defects in MMR increase mutation rates leading to the development of tumors. The MMR system consists of four stages: 1) mismatch

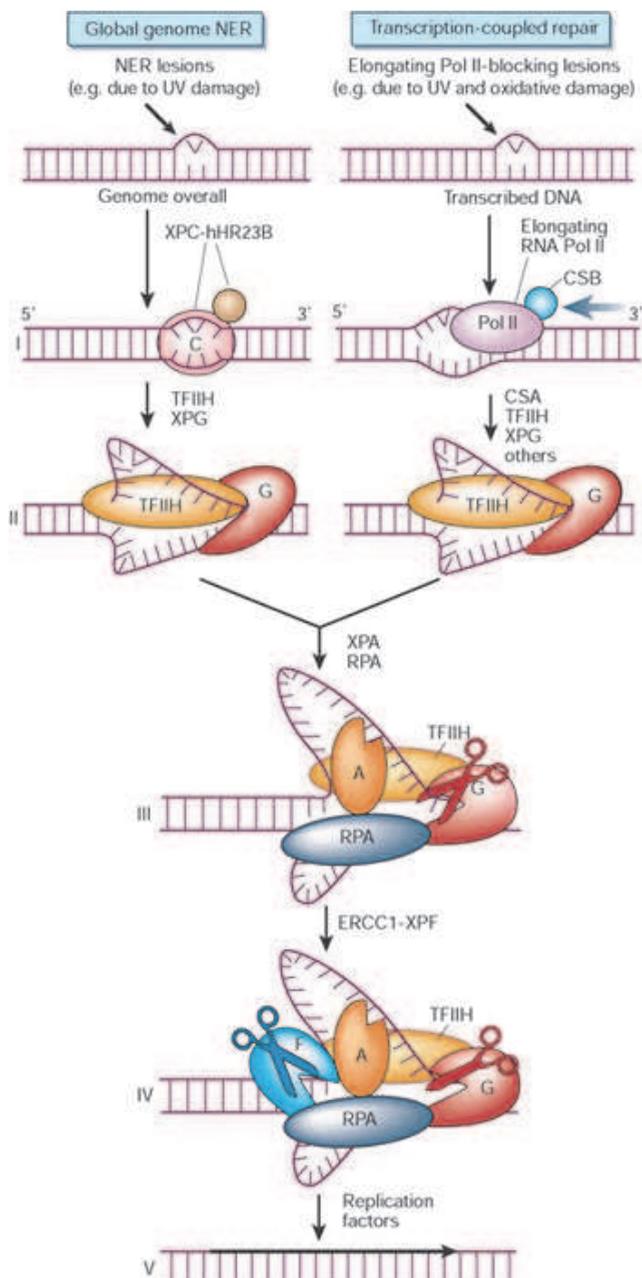


Fig. 3. Two NER subpathways exist with partly distinct substrate specificity: global genome NER (GG-NER) surveys the entire genome for distorting injury, and transcription-coupled repair (TCR) focuses on damage that blocks elongating RNA polymerases. Figure taken from Hoeijmakers<sup>30</sup>

recognition, 2) recruitment of MMR factors, 3) identification and degradation of the mismatch containing strand, and 4) synthesis of the new strand (Figure 4). HNPCC is an inherited disease caused, in 60% of cases, by germline mutations in *hMLH1* and *hMSH2* genes. Defects in *hMSH6* cause late-onset HNPCC. Mice that are completely MMR deficient show a normal development<sup>28</sup> but are cancer-prone. Homologous recombination (HR) has been proposed to play a role in repairing double-strand breaks as a result of cisplatin-induced crosslinks.<sup>23</sup> HR is not discussed in this chapter but different DNA repair systems are discussed in an excellent review by Hoeijmakers.<sup>30</sup>

Gene name	other name	Function
ERCC1	ERCC1	Forms complex with XPF for 5'-incision
XPA	XPA	Verifies DNA damage
XPB	ERCC3	3'->5' helicase
XPC	XPC	Sensor for DNA damage
XPB	ERCC2	5'->3' helicase
XPE	DDB2	Damage specific binding
XPF	ERCC4	Forms complex with ERCC1 for 5'-incision
XPG	ERCC5	3'-incision
CSA	ERCC8	Forms complex with CSB in TCR
CSB	ERCC6	Binds stalled polymerase II in TCR

Table 1. Key enzymes in NER

## 6. Cellular response to platinum-DNA adducts

As described above, cells possess several DNA repair mechanisms for removing Pt-DNA adducts. The tumor specificity of oxaliplatin and cisplatin is not fully understood. Although both drugs cause DNA damage, the DNA repair mechanism of the host cell responds differently to these drugs. For example, damage caused by oxaliplatin is restored by the nucleotide excision repair mechanism, whereas the mismatch repair mechanism is also active to restore damage caused by cisplatin.<sup>10,54</sup> So, what is the underlying mechanism that makes certain tumors more sensitive to cisplatin than to oxaliplatin? Resistance to platinum anticancer agents can result from decreased accumulation, increased inactivation by glutathione, or an increased ability of cells to tolerate Pt-DNA adducts.<sup>1</sup> The ability of cells to repair platinum-induced DNA lesions is known to be an important factor in cisplatin cytotoxicity.<sup>13</sup>

Interestingly, oxaliplatin induced DNA damage is as effectively repaired as cisplatin-induced damage, as shown in plasmid reactivation experiments.<sup>71</sup> The nucleotide excision repair has an extremely broad specificity, therefore it is not surprising that NER does not discriminate between oxaliplatin and cisplatin DNA adducts.<sup>66</sup> The MMR system, however, is a crucial element in the repair of cisplatin-induced damage as this system does not appear

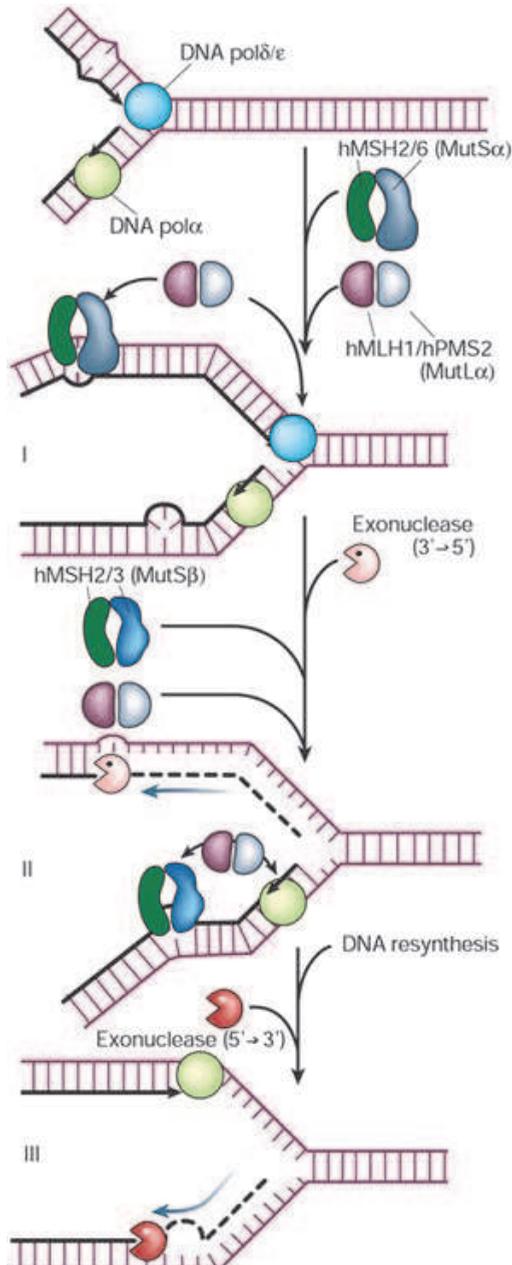


Fig. 4. Four principal steps in MMR can be delineated: (1) mismatch recognition; (2) recruitment of additional MMR factors; (3) search for a signal that identifies the wrong (newly synthesized) strand, followed by degradation past the mismatch; and (4) resynthesis of the excised tract. Figure taken from Hoeijmakers<sup>30</sup>

to recognize diaminocyclohexane-containing platinum<sup>64</sup> DNA-adducts such as those caused by oxaliplatin. Although cells definitely respond differently to oxaliplatin and cisplatin, the mechanism behind that has still to be elucidated. Many studies that investigate the role of DNA repair mechanism in repairing DNA crosslinks, use cisplatin or mitomycin C as a model to induce such crosslinks.<sup>57</sup> For instance the human ovarian cell line A2780 is sensitive to cisplatin but resistant to oxaliplatin.<sup>48</sup> In this study it was shown that ERCC1 (a key enzyme in NER) mRNA is upregulated after exposure to cisplatin. Whether ERCC1 mRNA levels are upregulated after exposure to oxaliplatin, is not known.

## 7. The role of DNA repair enzymes in platinum resistance

There is growing evidence that activity of DNA repair enzymes contributes to the interindividual differences in the anti-tumor effect of platinum drugs. Activity of DNA repair system is affected by functional SNPs in key enzymes, but also expression levels of such enzymes might differ between individuals. High levels of ERCC1 mRNA are associated with worse outcome in patients with bladder cancer treated with oxaliplatin.<sup>3</sup> An SNP in exon 4 of *ERCC1* (rs11615) was associated with better survival in non-small cell lung carcinoma treated with cisplatin,<sup>34</sup> as was in colorectal cancer patients treated with oxaliplatin.<sup>62,81</sup> The *ERCC2* gene (*XPD*) is located at the same chromosome as *ERCC1* and multiple non-synonymous SNPs in *ERCC2* have been found associated with diminished DNA repair capacity.<sup>74</sup> Since rs11615 is a silent SNP (not causing amino acid change) the association with diminished DNA repair capacity is suggested to be due to low ERCC1 expression caused by a linked SNP (rs3212986) in its 3'NTR region.<sup>34</sup> In vitro studies to test this hypothesis have not been performed. Interestingly, another gene in a reverse orientation, overlaps with ERCC1 3'NTR, and a role for this gene in DNA repair has been suggested.<sup>69</sup> This gene was identified in 1999 as a CD3 $\epsilon$  binding protein in T-cells and was therefore named CAST (CD3 $\epsilon$ -associated signal transducer).<sup>86</sup> Later, this gene was identified as a subunit of RNA Polymerase I.<sup>60</sup> While the exact function of this Pol I-specific subunit is unknown, in mammalian cells the interaction with the activator of Pol I transcription, UBF, suggests a role for this subunit in facilitating the transition from transcription initiation to elongation at promoter escape.<sup>59</sup> In another model it has been proposed that conformational changes in the Pol I enzyme complex through CAST convert the Pol I into a processive enzyme complex.<sup>60</sup> Since the 3' NTR of ERCC1 overlaps with CAST open reading frame, rs3212986 causes an amino acid change in CAST in a putative nuclear localization signal. It is likely that this SNP affects CAST function instead of ERCC1 expression. The hypothesis that CAST function is related with DNA repair is strengthened by its chromosomal location, between *ERCC1* and *ERCC2* (Figure 5).

An effect of platinum-based drugs on RNA polymerase I transcription is not without precedent. Cisplatin-induced platinum adducts interact with proteins that contain high-mobility-group (HMG) domains, such as UBF, an activator of Pol I transcription. UBF was able to bind cisplatin-modified DNA more avidly than unmodified DNA<sup>12</sup> and caused a redistribution of UBF in the nucleolus and a block of rRNA synthesis in human cells.<sup>37</sup> Furthermore, UBF expression could increase the cell sensitivity to the chemotherapeutic reagent cis-diaminedichloroplatinum,<sup>32</sup> perhaps by inhibiting repair of the DNA adducts. In addition, SNPs in CAST gene are associated with adult onset glioma<sup>11,85</sup> and treatment outcome in multiple myeloma patients undergoing bone marrow transplantation.<sup>79</sup> In view of the model where Pol I transcription of the rRNA genes is a sensor for DNA damage and

of the intricate association of CAST with Pol I, rs3212986 could result in a CAST-Pol I complex with a decreased capacity to elicit a DNA damage response. In those cells that carry this particular SNP, damage is therefore not efficiently repaired and this might result in increased cytotoxicity to platinum drugs, impairment of tumour growth and hence an increased patient survival.

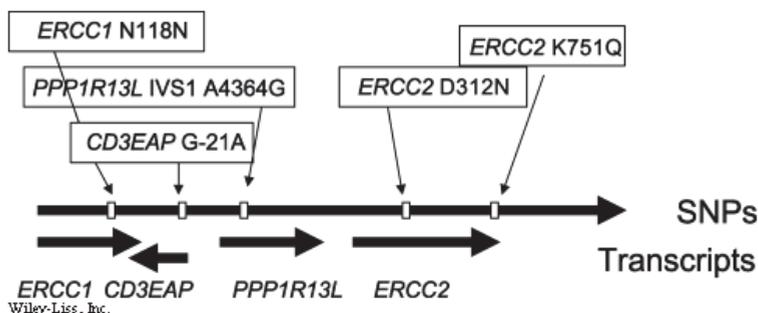


Fig. 5. Graphical presentation of the studied SNPs on chromosome 19. The *ERCC1* polymorphism is silent and does not result in an amino acid substitution. The *CD3EAP* polymorphism is G to A transversion in the 5' untranslated region of the mRNA. The *PPP1R13L* polymorphism is in intron 1 of the *PPP1R13L* gene. The *ERCC2* D312N polymorphism gives rise to the Asp to Asn amino acid substitution in position 312 of *ERCC2*. *ERCC2* K751Q gives rise to the Lys to Gln substitution in position 751 in *ERCC2*. Figure taken from Vangsted et al<sup>79</sup>

## 8. Pharmacogenetic research of DNA repair genes in practice

Cisplatin pharmacogenetics have been studied in esophageal cancer patients where several SNPs in NER were investigated. Two SNPs in *ERCC1* and the SNP in *ERCC1* 3'-NTR (or CAST as discussed above) were found associated with improved overall survival.<sup>6</sup> In testicular cancer cells, cisplatin sensitivity has been associated with low expression of *ERCC1*, however no SNPs were investigated in this study.<sup>77</sup> Low expression of *ERCC1* was also associated with oxaliplatin cytotoxicity in colorectal cancer cell lines when cetuximab (monoclonal antibody raised against EGFR) was co-administered.<sup>2</sup> Platinum resistant ovarian cancer patients receive carboplatin together with gemcitabine<sup>49</sup> that appeared to inhibit carboplatin induced interstrand crosslink repair.<sup>4,47</sup> The role of *ERCC1* in platinum treatment of non-small cell lung cancer with emphasis on carboplatin, has been reviewed by Vilmar and Sorensen.<sup>82</sup> Recently, an explorative study has been performed to identify novel candidate genes related to oxaliplatin efficacy and toxicity in colorectal cancer patients, using a DNA repair array.<sup>43</sup> Only *ERCC5* (another factor in NER) and *ATM* (general responder to DNA damage) were found associated with clinical response. Discrepancies in association with SNPs in other DNA repair enzymes, present on the array, are discussed in this paper.

## 9. Summary

Since the entire human genome has been sequenced and 3,000,000 (1 in 1000 nucleotides) SNPs have been identified, more and more research is being performed to test effects of

specific SNPs. Pharmacogenetic research is particularly focused on SNPs with a high allele frequency and an altered response to drugs. Many association studies have been performed and SNPs in genes encoding for drug transport, uptake, metabolism, detoxification and DNA repair, are found to be related to drug response. SNPs in coding regions may alter gene function, however, associated SNPs are not causal per se but may be linked to another, yet unidentified, linked SNP. The ultimate goal of pharmacogenetic research is to predict an individuals' response to drug therapy and subsequently adapt the therapeutic strategy. Peripheral blood can be taken to isolate chromosomal DNA and to genotype for specific SNPs, although tumor DNA might contain more mutations. In addition, expression levels of key enzymes may differ in tumor cells compared to normal cells. An approach to measure mRNA expression or to genotype tumor DNA could be the isolation of circulating tumor cells from peripheral blood. Whether this is feasible and cost effective for diagnostic healthcare should be investigated. In conclusion, more research is needed before any of the associated SNPs in DNA repair enzymes could be used to predict an individual response to a specific platinum-drug.

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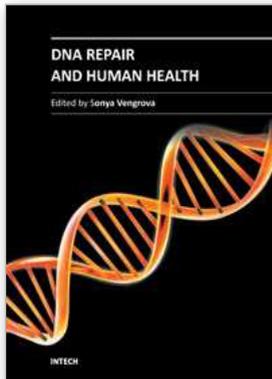
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## **DNA Repair and Human Health**

Edited by Dr. Sonya Vengrova

ISBN 978-953-307-612-6

Hard cover, 792 pages

**Publisher** InTech

**Published online** 26, October, 2011

**Published in print edition** October, 2011

Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

### **How to reference**

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Tahar van der Straaten, Leon Mullenders and Henk-Jan Guchelaar (2011). Pharmacogenetics of Cancer and DNA Repair Enzymes, DNA Repair and Human Health, Dr. Sonya Vengrova (Ed.), ISBN: 978-953-307-612-6, InTech, Available from: <http://www.intechopen.com/books/dna-repair-and-human-health/pharmacogenetics-of-cancer-and-dna-repair-enzymes>

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